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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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VIVIANA AMZEL, PH.D.
ARTER & HADDEN
CITICORP BUILDING
725 SOUTH FIGUEROA STREET
LOS ANGELES CA 90071

EXAMINER	
EPPS,J	
ART UNIT	**PAPER NUMBER**
1635	18

DATE MAILED: 11/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/093,972	Johnathan Nyce
Examiner	**Group Art Unit**
Janet Epps	1635

☒ Responsive to communication(s) filed on *May 11, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *108-219* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *108-219* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Status of Claims

1. The rejection of claims 1-107 set forth in the prior Office Action are withdrawn in response to Applicant's cancellation of these claims.

2. Newly added claims 108-219 are currently pending on the instant application.

Response to Amendment

3. The amendment filed 8/29/00 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant's have indicated that the present application is related to Application 08/472,527, now US Patent 6,040,296, US Application 08/757,024, now US Patent 6,025,339, Application 08/472,527, 08/474,497, now US Patent 5,994,315, and Application 09/016,464. In addition, Applicants have amended the specification to add targets and exemplary oligonucleotides that were disclosed in Application 08/474,497. However, since Applicants did not incorporate the disclosure of 08/474,497 by reference in the original specification, the original specification does not support Applicant's amendment. At the Examiner's request, Applicants have added a full description of the surfactants mentioned by Trademark name in the specification, namely TRITON X-100, BRIJ 35, ALEC, SURVANT, EXOSURF, ATOVAQUONE. However, in addition to amending the specification regarding the Trademarked compounds listed above, Applicants have also included a

description of other surfactants not discussed in the original specification. Namely, colfoceryl-cetyl alcohol-tyloxapol, colfosceril palmitate, cetyl alcohol and neutral lipids.

Applicant is required to cancel the new matter in the reply to this Office action.

Substitute Specification

4. Substitute specification filed 5/11/00 does not comply with 37 CFR 1.125. See MPEP § 608.01(q) and § 714.20. Specifically, the Substitute specification was not accompanied by a statement that the substitute specification includes no new matter.

Sequence Listing

5. The Declaration submitted under 37 CFR 1.821(f) is unacceptable, Applicant's representative stated that the paper and computer readable copies of the sequence listing submitted in accordance with 37 CFR 1.821(c) and 1.821(e), "include no new matter and are, to the best of the applicant's knowledge, the same as the sequence submitted with the application as filed, except for sequence 997-1035, which sequences have been added to the application supported by the disclosure of the parent application USSN 08/474,497". This statement is unacceptable, as indicated above the original disclosure does not incorporate the disclosure of 08/474,497. Applicants were requested to provide a statement that the content of the paper and computer readable copies are the same, and where applicable, include no new matter, as required by 37 CFR 1.821(e)-(g) or 1.825(b) or 1.825(d).

6. The reply filed 5/11/00 is not fully responsive to the communication mailed 01/04/00 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report.

Response to Arguments

7. Applicant's arguments with respect to claims 1-107 have been considered but are moot in view of Applicant's cancellation of these claims.

In response to the rejection of claims 1-107 under 35 USC 112, first paragraph, set forth in the prior office action, Applicants argue that the specification as filed fully enables the claimed method which comprises a broad administration of oligos antisense to any target gene or RNA. Applicants claim that the examples in the specification as filed and the Declarations submitted my applicants are sufficient to provide enablement for the claimed invention. However, the compositions used for administration to animals for the treatment of an airway disease are all in aerosolized formulations. The compounds of the instant invention are formulated in a composition comprising a surfactant. According to Applicants the presence of the surfactant in these formulations render these compositions novel over the aerosolized compositions previously claimed in Applicant's patents. Applicant's reference to the Declarations of Nyce are therefore not applicable since the experiments demonstrated by Nyce do not comprise the use of antisense formulations with a surfactant. Furthermore, the specification as filed has only exemplified one specific antisense oligonucleotide demonstrating its effectiveness *in vitro* reduce the expression human adenosine receptor mRNA, and the effectiveness of this particular antisense oligonucleotide to ameliorate asthmatic symptoms in rabbits. However, the formulations utilized in the examples are aerosolized formulations, and do not comprise a surfactant. In addition, applicants have not demonstrated that

the claimed surfactant necessarily counters low levels of natural surfactant or enhances the uptake of the oligo through the lung.

Claim Objections

8. Claim 172 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 172 recites "[t]he kit of claim 167, further comprising .... means for delivery thereof, and instructions", however the kit of claim 167 comprises both a means for delivery and instructions for its use.

9. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 178 (2nd claim 178) through 218 have been renumbered 179-219.

10. Claim 185 recites "administration and renal", and claim 199 recites "[nucleic acids]bases".

Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. In the reply filed 5/11/00, applicant has used underlining and bracketing in such a manner that it is unclear to the examiner whether the underlining and bracketing is intended to appear in the

patent. If underlining and/or bracketing is intended to appear in the claims in the published patent, such intention must be clearly indicated in applicant's reply to this notice.

New Grounds of Rejection Necessitated By Amendment

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 108-109, 113-115, 118-119, and 208 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 108 recites "the initiation codon", "the coding region", "the 5' or 3' intron-exon junctions", "the uptake", there is lack of antecedent basis for these limitations in this claim.

Claim 108 recites "throughout he lung", the use of the term "he" in this phrase is likely to be a grammatical mistake. The correct term is likely to be "the".

13. Claims 109, and 113-115 recite the limitation "the composition" in claim 108. There is insufficient antecedent basis for this limitation in claim 108. These claims should read the "pharmaceutical composition of claim 108".

14. Claims 118-119, and 208 recite "wherein the pyrimidines and purines are substituted at a position selected from the group consisting of positions 1, 2, 3, 4, 7, and 8. The exact positions of substitution that Applicant is referring to are vague and indefinite since is unclear where these

positions are in both pyrimidines and purines, pyrimidines and purines are different classes of molecules with different positions that are potentially substituted.

15. Claim 120 recites the limitation "the universal base" in claim 119. There is insufficient antecedent basis for this limitation in the claim.

16. Claim 134 recites the limitation "the carrier" in claim 108. There is insufficient antecedent basis for this limitation in this claim.

17. Claim 156 recites the limitation "the mucleic acid" in claim 155. There is lack of antecedent basis for this limitation in the claim. This limitation is likely to be a grammatical error, the proper limitation is likely to be "the nucleic acid".

18. Claims 164-165 recite "cell internalized or up-taken agent", these claims are vague and indefinite since the metes and bounds of what this recited phrase means is unclear.

19. Claim 169 recites the limitation "the solvent" in claim 167. There is insufficient antecedent basis for this limitation in the claim.

20. Claim 173 recites "comprises least one", this phrase is vague and indefinite since it is unclear what this phrase is intending to encompass. It is likely that this phrase was intending to recite "comprises at least one".

21. Claim 173, line 11, recites "and mixtures of the nucleic acids, their combinations and their salts." Claim 173, and those claims dependent therefrom, appear to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no

uncertainty or ambiguity with respect to the question of scope or clarity of the claims. The metes and bounds of this Markush group is indefinite because it is unclear if the members of this group are mutually exclusive. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat. 1925).

22. Claim 175 recites "cancers that are or will be treated with radiation", this phrase is vague and indefinite since it is unclear which "cancers" are referring to since this phrase encompasses forms of "cancers" that have yet to be discovered.

23. Claim 179 (renumbered 2nd claim 178) recite the limitations "the agent" and "the adenosine receptor" in claim 174. There is insufficient antecedent basis for this limitation in the claim.

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 108-219 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using pharmaceutical compositions comprising antisense oligonucleotides targeting adenosine receptor mRNA effective in treating an asthmatic condition provoked by the administration of adenosine, does not reasonably provide enablement for the treatment of all airway diseases, allergies, lymphomas or carcinomas of the colon, breast, lung, pancreas, kidney, melanoma, liver, lung, breast or prostate cancer or metastatic cancer by administration of pharmaceutical

compositions comprising antisense targeting any other mRNA target. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 108-172 are drawn to "a pharmaceutical composition comprising a surfactant; and a nucleic acid which comprises an oligonucleotide (oligo) effective to alleviate bronchoconstriction, allergy (ies) or inflammation, the oligo being antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding an adenosine A1, A2a, A2b, or A3 receptor or antisense to their respective mRNA; combinations of the nucleic acids; and a surfactant...", and kits comprising said pharmaceutical compositions.

Claims 173-219 read on an in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to the airways of a subject an aerosol composition comprising a nucleic acid which comprises at least one oligonucleotide effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, bronchoconstriction, allergies, and/or inflammation, and a disease or condition associated with lung inflammation, cancers of the lung, breast, prostate, metastatic cancer, and cancers that are or will be treated with radiation, etc.

The specification as discloses only antisense oligonucleotides targeting mRNAs encoding adenosine receptors There are no guidelines or instruction to teach one of skill in the art to make and or use a pharmaceutical composition, comprising an antisense targeting any and all genes, to alleviate the diseases recited in the instant invention. The specification discloses only one functional antisense

targeting adenosine receptors in aerosolized form that are effective in alleviating bronchoconstriction, allergies and inflammation.

The specification fails to provide an enabling disclosure for how to treat bronchoconstriction, inflammation, allergies, and the multiple forms of cancer recited in the instant invention by the administration of a pharmaceutical composition comprising an antisense oligonucleotide targeting any gene. In the absence of a comprehensive understanding of the role of a particular gene product in the etiology of a given disease state, it is impossible to predict if the inhibition of that gene product would yield any useful or efficacious results. Furthermore, even if the role of a given gene product is well understood, due to the unpredictability regarding the behavior of antisense based therapeutics that one cannot predict whether an oligonucleotide targeted to the gene in question would effectively reduce its expression *in vivo*. The design of antisense oligonucleotides to a target gene requires knowledge of the nucleic acid structure of the gene, the specification as filed provides only a description of nucleic acids targeting adenosine A1, A2B, and A3 receptor mRNAs. Crooke describes a variety of factors that influences the activity of antisense based compounds that must be considered when designing an antisense oligonucleotide. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors such as: length of the oligonucleotide, modifications to the oligonucleotide structure, the nucleotide sequence of the oligonucleotide and the type of cell the antisense is administered to. Furthermore, Crooke describes the influence of non-antisense effects, for example, phosphorothioate oligonucleotides tend

to bind to many proteins, this protein binding may influence cell uptake, distribution, metabolism and excretion of the oligonucleotide. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable.

The specification as filed does not enable anyone of skill in the art to practice the instant invention throughout the full scope of the claimed invention. This conclusion is based upon the known unpredictability in the art regarding antisense based therapeutics, the lack of guidance, direction or description provided by the specification, the limited number of working examples provided by the specification, the breadth of the claims, and the amount of experimentation need to practice the invention.

Claim Rejections - 35 USC § 102

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

27. Claims 108-111, and 173-175 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,514,788 (1996) Bennett et al.

Claims 173-175 are drawn to pharmaceutical compositions comprising a surfactant, and an antisense oligonucleotide effective to alleviate bronchoconstriction, allergies, or inflammation.

Bennett et al. teach a method of treating diseases, including asthma (see Abstract and col. 3, lines 15-18), and a pharmaceutical composition for use in such a method, comprising administration of antisense oligonucleotides targeted against an mRNA encoding ICAM-1, VCAM-1, or ELAM-1 (see col. 5, lines 21-29); the antisense oligo, which may comprise nucleoside linkages such as phosphorothioates, phosphotriesters or methyl phosphonates and contains approximately 10% adenosine, may be administered topically, by inhalation, in a formulation that may include sprays (col. 7, lines 44-53). Bennett also discloses antisense formulations for use in a murine model comprising DOTMA/DOPE (dioleyloxypropyl-N,N,N-trimethylammoniumchloride dioleylphosphatidylethanol-amine; example 19, col. 25). The antisense oligonucleotides of Bennett comprise variable adenosine content, one particular antisense oligonucleotide disclosed by Bennett et al. comprises 5% Adenosine, ISIS #2679, which functions to inhibit the expression of ELAM-1 (see col. 21, Table 3). Administration of the compounds of Bennett et al. may be topically (including ophthalmically,

vaginally, rectally, intranasally), orally, by inhalation, or parenterally, for example by intravenous drip, subcutaneous, intraperitoneal or intramuscular injection. [According to Applicant's arguments regarding the third anticipation rejection set forth in the prior office action, Bennett et al. does not disclose or suggest an aerosol composition nor does this reference teach treating a subject by administering to his/her airways said aerosol composition. As stated above the formulations of Bennett et al. comprise spray formulations which encompasses aerosol formulations, and Bennett et al. teach delivery by inhalation and intranasally. These modes of delivery comprise delivery to the lungs of a subject.]

Therefore, Bennett et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Conclusion

28. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

November 6, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER